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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,693	KAEMMERER, WILLIAM F.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,10-18 and 20-89* is/are pending in the application.

4a) Of the above claim(s) *2-4,6-8,11-13,15-18,20-23 and 26-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10,14,24,25 and 85-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

Applicant's response filed 6 November 2006 has been considered. Rejections and/or objections not reiterated from the previous Office Action mailed on 7 August 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

With entry of the amendment of 6 November 2006, Claims 1-4, 6-8, 10-18, and 20-89 are pending. Claims 2-4, 6-8, 11-13, 15-18, 20-23, and 26-84 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species, there being no allowable generic or linking claim. Claims 5, 9, and 19 have been cancelled by applicant.

Claims 1, 10, 14, 24, 25, and 85-89 are currently under examination.

Non-compliant Amendment

Applicant is reminded that 37 CFR §1.121(c)4)(i)—Manner of making amendments in application—states that "No claim text shall be presented for any claim in the claim listing with the status of 'canceled' or 'not entered.'" In the instant case, Applicant has cancelled claims 5, 9, and 19, but presents the text of claims 5, 9, and 19 in the listing of claims submitted on 11/6/06. Further, in the Remarks, page 11, Applicant states that claims 5, 9, and 19 have been

"withdrawn" rather than cancelled, as shown in the claim listing, making the true status of the claims unclear. Clarification and/or correction is required.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, U.S. Provisional application 60/429,387, upon which benefit is claimed fails to provide adequate support under 35 U.S.C. 112 for claims drawn to medical systems comprising small interfering RNA, Claims 1, 5, 9, 10, 14, 19, 24, 25, and 85–89. The instant application clearly defines small interfering RNA (pages 14-15) as "double stranded RNA agents" that are "used to trigger RNA interference." As ordinarily used in the art, "small interfering RNA" normally refers to double stranded RNAs, which operate by a different biochemical pathway than ribozymes and antisense (single stranded) RNAs. Thus, antisense, ribozymes, and small interfering RNA are considered to represent distinct molecular agents. The earliest filed priority document in which adequate support is provided for medical systems comprising small interfering RNA is U.S. Provisional application 60/444, 614, filed 2/3/03. If applicant believes that support for the instant claims, drawn to medical systems comprising small interfering RNA agents, is present in the earlier filed priority document, applicant must, in responding to this Action, point out with particularity, where such support may be found.

Applicant's response and amendment to the specification in the response filed 11/6/06, is acknowledged.

Applicant is notified that a cancellation of a benefit claim to a prior application may be considered as a showing that the applicant is intentionally waiving the benefit claim to the prior

application in the instant application. If the applicant later files a petition to accept an unintentionally delayed claim to add the benefit claim to the prior application in the same application from which the benefit claim was canceled, the Office may refuse to accept such benefit claim because the delay was not unintentional. See MPEP 201.11.

Claim Objections—new

Claims 1 and 24 are objected to because of the following informalities.

Claim 1 recites a "human live patient." The limitations "live" and "patient" are redundant. Given that the method is directed to a method for treating a disorder—ataxia—it is implied that the patient being treated is still living. The term "patient" is reasonably interpreted as a living person or animal who receives treatment, and would not reasonably embrace deceased subjects for which the concept "treatment" holds no meaning and has no apparent utility. Thus, the term "live" in the phrase "human live patient" is not only awkward but redundant.

Claim 24 is objected to because of the recitation "into an intracranial access port." The reference lacks clear antecedent basis, as claim 1 does not clearly recite a "port" and there is no indication of the relationship of a "port" with any of the other elements recited in claim 1. Correction and/or clarification is required.

Claim 85 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recites the medical system of claim 1 wherein said small interfering RNA is able to inhibit expression of ataxin-1 protein. However, claim 1, as amended,

already recites a small interfering RNA capable of reducing the amount of ataxin-1 protein produced in a cell (see part c of claim 1).

Clarification and/or correction is required.

Claim Rejections - 35 USC § 112, second paragraph—withdrawn

The rejections of Claims 1 and 89 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, second paragraph—new

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10, 14, 24, 25, and 85-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As amended, independent claim 1 recites "the small inhibitory RNA" in part d. There is insufficient antecedent basis for this limitation in the claim. The recitation appears to be referring to "interfering RNA." Dependent claims 10, 14, 24, 25, and 85-89 are rejected therefore due to their dependence on claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph—new

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 14, 24, 25, and 85-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendment to the claims submitted on 11/6/06, introduces the limitation "at least about 9 bp downstream of a transcription start site of said gene" into independent claim 1.

MPEP 2163, Section II, Part A, states in part that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims.

In the instant case, Applicant has not pointed out where the amended claim is supported, nor does there appear to be a written description of the claim limitation "at least about 9 bp downstream of a transcriptioin start site of said gene" in the application as filed (MPEP 2164.04).

That is, a review of the application fails to find explicit, implicit, or inherent support for the instant limitation.

Accordingly, the instant claims as a whole are rejected for lack of written description support.

Claim Rejections - 35 USC § 112, first paragraph—withdrawn

The rejection of Claims 1, 10, 14, 24, 25, and 85-89 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicant's arguments, which are found persuasive.

Double Patenting—maintained with new reference

Claims 1, 10, 14, and 25 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 (US 2005/0048641) in view of Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed; and Serra et al. (1996) *Medical Image Analysis* 1(4):317-329.

As amended on 11/6/06, Claim 1 now recites "a mapping means for locating a predetermined location in the brain of the patient." (Underline added) Thus, the body of the claim now specifically refers to the "human live patient" recited in the preamble, requiring that the "mapping means" be one capable of determining the location of structures in the human brain.

Accordingly, Serra et al. is now applied in the instant rejection. Paxinos et al. is removed as it is directed to mouse brain.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Copending application No. 10/962,732 and the instant application are both directed to a medical device, or system, for transfusing interfering RNA (siRNA) into tissues and cells in living organisms, including humans. Claim 1 of the instant application recites a medical system for treating a neurodegenerative disorder "in a patient," comprising an intracranial access device, a mapping means, a deliverable amount of siRNA or vector encoding siRNA, and a delivery means. Claims 9 and 10 limit claim 1 by stating that the access device is a catheter or access port. Claim 19 limits claim 1 by stating that the siRNA targets SCA1 mRNA. Claim 25 limits claim 1 by stating that the delivery means is an infusion pump.

Claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 recite a similar system for delivering small interfering RNA targeted to a gene, SCA1, associated with a neurodegenerative disease. Claim 7, the base claim, recites a system comprising an implantable infusion pump, a reservoir, a fluid comprising an RNAi agent, and a catheter. The implantable infusion pump is defined as being either implantable or external, may have a port into which a needle can be inserted to inject a therapeutic agent, and may further have a catheter, and a catheter port (paragraph 24) for delivering an RNAi agent to a specific location in the brain. Paragraph 29 describes a specific embodiment of the claimed system; namely, intraparenchymal and intracerebroventricular delivery devices (illustrated in Fig. 3) for delivering agents to the brain, and clearly embodies an access port and catheter. Thus, the device claimed by claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 may serve to deliver siRNA

intracranially to different regions of the brain and is, therefore, considered to encompass "medical systems" such as those claimed in the instant application.

Furthermore, Applicant states on page 28 of the instant application (10/721,693) that "The envisioned route of delivery is through the use of implanted, indwelling, intraparenchymal catheters that provide a means for injecting small volumes of fluid containing AAV or other vectors directly into local brain tissue." On page 29 of the instant application, Applicant states that "...the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Patent No. 5,735,814 and 6,042,579..."

Copending Application No. 10/962,732 does not claim a "mapping means" or means for locating a predetermined location in the brain. However, it would be obvious to one of skill in the art to combine the teachings of copending Application No. 10/962,732 with those of a standard anatomical atlas such as that of Cahill et al. and Serra et al., who provide methods for determining coordinates for different brain locations, as well as a sophisticated neurosurgical system for implementing treatment of human brain condition.

Accordingly, one of skill in the art would conclude that the invention defined in the instantly claimed invention of this application (No. 10/852,997) is an obvious variation of the invention defined in copending Application No. 10/721,693 since each of the required elements are present and each of the devices or systems is clearly intended to serve as a system for delivering small interfering RNA (specifically siRNA targeting SCA1 mRNA) intracranially to treat a neurodegenerative disease.

Thus in the absence of evidence to the contrary, the instantly claimed invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's arguments

Applicant's request for postponement of rejection under this section is non-responsive. The rejection is maintained until such time as it is the only rejection in the application.

Double Patenting—new

Claims 1, 10, 14, 24, 25, 85-87, and 89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over at least claims 1-17 and 29 of copending Application No. 10/962732. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a system comprising an implantable infusion pump; a reservoir operably coupled to the pump; a fluid comprising an RNA inhibitory agent, the fluid being housed in the reservoir; a catheter operably coupled to the pump, the catheter having a delivery region through which the fluid may be delivered; and a means for controlling the rate at which the fluid is delivered when the pump is implanted in a patient, wherein the RNA agent may be targeted to SCA1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103—new

As now amended, Claims 1, 10, 14, 24, 25, 85–87, and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010; Driscoll et al. (WO 01/49844); Cahill et al.; Serra et al. (1996) *Medical Image Analysis* 1(4):317-329; Morel et al. (1997) *J. Comparative Neurology* 387:588-630; Clark et al. (1997) *J. Neuroscience* 17:7385-7395; Salehi et al. (1999) *J. Neural Transm.* 106:955-986; Whitesell et al. (1993) *Proc. Natl. Acad. Sci.* 90:4665-4669; Davidson et al. (US Patent Application Publication 2004/0023390); Matilla et al. (1998) *J. Neuroscience* 18:5508-5516; Exhibit A: NCBI published mRNA sequence of SCA1 (Mar. 24, 1999); and Caplen et al. (2002) *Human Molecular Genetics* 11:175-184.

As amended on 11/6/06, Independent Claim 1 now recites in part b "a mapping means for locating a predetermined location in the brain of the patient." (Underline added) Thus, the body of the claim now specifically refers to the "human live patient" recited in the preamble, requiring that the "mapping means" be one capable of determining the location of structures in the human brain.

As amended, claim 1 also requires that the system comprise a deliverable amount of a small interfering RNA capable of reducing the amount of ataxin-1 protein in cells in the brain for treating spinocerebellar ataxia type 1 in the brain of said human patient.

Claim 1 further requires that the "small inhibitory RNA" be complementary to a target sequence at least about 9 bp downstream of a transcription start site of a gene encoding ataxin-1.

Accordingly, the amendments narrow the scope of the invention to methods for treating spinocerebellar ataxia type 1, rather than any neurodegenerative disorder.

In the previous Action, Applicants were notified that the claim limitation "a mapping means for locating a predetermined location in the brain of a patient" is being treated under 35 U.S.C. 112, sixth paragraph, as a means for performing a specified function, and that the limitation shall be construed to cover the corresponding structure or material described in the specification and equivalents thereof.

As explained above, the instant application does not explicitly or implicitly describe any structure or material corresponding to the recited "mapping means." The Examiner is therefore giving the recitation its broadest reasonable interpretation. A mapping means for locating a predetermined location in the brain of a patient, including a human patient, may reasonably be construed to include an anatomical atlas, electronic or printed, especially those designed to assist with neurosurgery and neurosurgical implants.

Applicant was advised that the recitation "means for locating a predetermined location in the brain" may be achieved simply by the mental act of 1) choosing a brain structure that one wishes to locate, based on, for example, its documented association with a particular neurodegenerative disorder (i.e., predetermining); and 2) referring to an atlas to determine its relative location and position in the brain (mapping or locating).

Applicant was reminded that the instant claim is not a method or process for performing gene therapy. The claim is drawn to an assembly or apparatus, comprising the four interrelated structures now recited in parts a-d of the claim.

In the previous Action, Applicants were notified that the preamble recitation "in a human live patient" recites "a patient," and does not specifically refer to a human patient. Thus, the preamble was not considered to limit the invention to the treatment of humans alone but simply recites an intended use.

With the current amendment, however, filed 11/6/06, part b of the claim specifically recites "the patient," which does limit the claim to human patients since it specifically refers back to the human patient in the preamble.

Accordingly, Paxinos et al. has been eliminated from the instant rejection, as it is directed to mouse brains.

In view of Applicant's amendment to the claim requiring that the target be at least about 9 bp downstream of a transcription start site, Caplen et al. is applied.

Response to Arguments

Applicant appears to argue that Xia et al. and Driscol et al. are incompatible, due to differences in the teachings with regard to the length of the siRNA and the information regarding the use of vector-encoded siRNAs or shRNAs. Applicant argues that Driscol does not teach methods for delivering siRNAs to the brains of patients or for determining locations in the brains of patients or any "intracranial access device." (Remarks, page 15).

Applicant argues that Cahill does not teach which brain structures are important for siRNA therapy or which structures express genes responsible for neurodegenerative disorders.

Applicant argue that Clark et al. does not discuss either siRNA therapy of spinocerebellar ataxia type 1, the criteria for siRNA selection or the specific siRNAs useful for treatment of spinocerebellar ataxia type 1 (Remarks, page 16).

Applicant argues that Whitesell does not disclose the brain structures natively expressing the ataxin-1 gene or provide any criteria for selection of the siRNAs such as those of the instant invention (Remarks, page 17).

Applicant argues that Davidson et al. is inapposite to the instantly claimed invention because Davidson et al. is limited to short, hairpin DNA encoding for shRNA, whereas Applicant's invention is not limited to the use of shRNA versus siRNA, let alone the use of RNA polymerase type two (pol II) promoters to drive the transcription of the shRNA, and because Davidson et al. does not claim a medical system for treating a patient, nor does it teach a method for administering the treatment of SCA 1 to the patient in terms of delivery devices, catheters, or specific anatomical regions to which to deliver the treatment, and because Davidson et al. does not provide any specific shRNA sequences that are effective at reducing the expression of the SCA1 mRNA in the patient.

Applicant argues that Matilla et al. only discloses that knocking out SCA1 gene function from embryonic conception does not cause an ataxic phenotype in the developing or adult animal, indicating that the SCA1 disease in humans is not due to a loss of the function of the SCA1 gene or ataxin-1 protein. Applicant argues that Matilla does not teach or suggest suppression of the expression of SCA1 in disease or suggest suppressing it to treat disease.

Finally, Applicant argues that Exhibit A: NCBI published mRNA sequence of SCA1 only provides a sequence for the ataxin-1 gene. However, this reference does not disclose or suggest

treatment of the spinocerebellar ataxia type 1, nor does this reference disclose the brain areas where this sequence is expressed, nor the portions of this sequence suitable for siRNA targeting.

Applicant's arguments filed 11/6/06 have been fully considered but they are not persuasive.

Xia et al., Driscoll et al., Cahill et al., Serra et al., Morel et al., Clark et al., Salehi et al., Whitesell et al., Davidson et al., Matilla et al., and Exhibit A: NCBI published mRNA sequence of SCA1 (Mar. 24, 1999) are relied on for the reasons of record.

Caplen et al. is further applied in view of Applicant's amendment to independent claim 1. Caplen et al. teach the use of siRNA to specifically inhibit the expression of genes encoding polyglutamine tract proteins, which Caplen et al. teach are associated with several neurodegenerative diseases. As part of their overall strategy, Caplen et al. teach that in designing effective siRNAs against polyglutamine tract-encoding genes, one may need to take into consideration the presence and location of CAG trinucleotide repeats in the genes themselves, since siRNA potency varies as a function of target site (page 181). Caplen et al. teach the use of siRNAs targeting sites in and around the start site of the open reading frame, implicitly teaching that one of skill in the art may need to design and test a number of siRNAs in and around the CAG repeats and start site to identify the most active and most potent siRNA.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Examiner submits that, when considered as a whole, the cited references teach and/or suggest a system for delivering SCA1-targeted siRNA into a predetermined location in the brain of a human to treat abnormal SCA1 gene expression associated with spinocerebellar ataxia, as explained in the previous Action.

It is not necessary for any one reference to teach each of the limitations of the claimed invention, for it is the combined teachings, taken as a whole, which render obvious the claimed invention as a whole.

Applicant's piecemeal analysis of the cited references ignores the implicit teachings of the combination of references, which, as whole, teach and reasonably suggest using RNAi technology to target and inhibit the expression of genes known to be associated with neurodegenerative disorders, including Parkinsons, Alzheimers, Huntington's, and spinocerebellar ataxia. Clark et al. are quite specific about the genetic abnormality behind spinocerebellar ataxia type 1, teaching that the disorder is most likely due to the expression of a mutant form of *SCA1*. In combination with Matilla et al., who teach that loss of expression does not cause disease, it would be clear to one of skill that a mutant form of SCA1 most likely gives rise to the disease.

It would have been obvious to one of skill in the art at the time the invention was made to design an siRNA specific for the mutant form of *SCA1,* to inhibit the expression of the mutant form of the protein, ataxin-1, and thereby treat the disease in afflicted persons. The motivation is within the knowledge of one skill in the art and the nature of the problem to be solved: to treat a neurological disease affecting the human population, wherein the disease is due to the abnormal expression of a gene, specifically an *SCA1* isoform. RNAi is well suited to this task, in that it is a

specific and potent method for inhibiting gene expression in cells and animals and is therefore well suited for therapeutic goals of treating virtually any disease arising from aberrant or overexpression. This general motivation combined with more specific motivation to target neurological diseases, as taught and exemplified by both Xia et al. and Driscol et al, and the more specific motivation to target the mutant allele of *SCA1,* as suggested by Clark et al., in combination with Matilla et al., provides sufficient motivation to make and use siRNA targeted to mutant SCA1 to eliminate faulty ataxin-1 protein and possible treat spinocerebellar ataxia.

Given that Xia et al. teach that siRNAs can be used to inhibit the expression of polyglutamine proteins (responsible for several neurodegenerative diseases) in the brains of mice, and that vectors expressing shRNAs hold promise as therapeutic tools and are useful for treating neurodegenerative diseases (Driscol et al.), and given that Clark et al. teach that spinocerebellar ataxia type 1 may be attributed to a polyglutamine expansion in the SCA1 gene, one of skill in the art would immediately extrapolate these teachings to systems for treating spinocerebellar ataxia, and would recognize that with the suitable equipment, guides, and/or methods, such as those taught by Serra et al. and Morel et al., one could deliver siRNA directly into the proper location of the human brain to treat abnormal SCA1 expression.

The design, synthesis, and application of siRNAs to treat neurological disorders by direct injection into the brain was well established in the art, as evidenced by Xia et al. and Driscol et al. Microsurgical procedures in human patients for purposes of correcting brain conditions were enabled, as evidenced by Serra et al. One of skill would have known which structures were particularly susceptible to ataxia, as evidenced by Clark et al.

Xia et al. state that interference of gene expression by small interfering RNA (siRNA) is now recognized as a naturally occurring biological strategy for silencing alleles during development in plants, invertebrates, and vertebrates. Xia et al. teach that long term inhibition of gene expression via siRNA, is effectively achieved by the introduction of vectors encoding siRNAs.

Applicant himself teaches that shRNAs are functionally identical to siRNAs and are processed to siRNAs in the cell upon expression in the cell (page 20, lines 5-20). Furthermore, the instant claims recite "small interfering RNA," which is an art-recognized term that is considered to embrace both two-stranded (bimolecular) and single-stranded, hairpin (unimolecular) structures. Thus, Applicants challenge of Davidson et al. as being limited to vectors encoding hairpins is not persuasive since the instant rejection is based on the fact that one of skill in the art would have been motivated to use small interfering RNA in all its forms to inhibit SCA1 expression. More particularly, one of skill in the art would have been motivated to use vectors encoding small hairpin RNA, as exemplified by Xia et al., Driscol et al., and Davidson et al.

Banfi et al. and the NCBI published sequence are cited as evidence that the target sequence of SCA1 was known in the prior art, which is a necessary prerequisite for the design and production of SCA1-specific siRNA or shRNA.

Thus in the absence of convincing evidence to the contrary, the invention as a whole would have been prima facie obvious at the time the invention was made.

Prior Art not relied upon

The following prior art is not relied upon, but is considered pertinent to applicant's disclosure.

- Elsberry (WO 97/40874), who teaches a system for treating neurodegenerative disorders by brain infusion.
- Elsberry et al. (US Patent 5,735,814) and Elsberry et al. (US Patent 5,814,014), who teaches devices for treating neurodegenerative disorders by brain infusion. On page 27 of the instant application, Applicant states that these devices can be used to deliver small interfering RNA in accordance with the present invention.
- "The StealthStation® Treatment Guidance System Fact Sheet" Medtronic, Inc. [online] [retrieved 12/1/06 from www.medtronic.com].

  The Fact Sheet states that the StealthStation Guidance system has been in use around the world as of July 2001 and provides a general description of the system. Applicant states in the Remarks filed 11/6/06, page 13, that the term "mapping means" especially with regard to accessing (e.g., surgically accessing) the brain of a live human patient is well-understood in the art. In fact, in 2001, Medtronic introduced a "mapping means" device termed the Medtronic NT StealthStation® TreonTM into the marketplace. This medical system further refines the computerized technologies of multi-dimensional imaging and navigation to enable neurosurgeons to precisely plan, re-plan and visualize a procedure as it proceeds deep within the brain for treating a neurological disorder such as for example SCA1 in a living human patient.

Response to Applicants' Arguments

Applicants' arguments presented on 11/6/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Allowable Subject Matter

Claim 88 is free of the prior art searched to date inasmuch as the prior art searched to date does not teach or reasonably suggest the medical system of claim 1 comprising a deliverable amount of siRNA comprising SEQ ID NO:1 or 2.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Louis Wollenberger
Examiner, Art Unit 1635
December 4, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER